REMARKS

Paragraph 5. Rejection of Claims 24-26, 28-32, 103, 105-109, 111-113, 115, 116, 118-122, 124, 125, 136-150 and 152-160 Under 35 U.S.C. § 112, First Paragraph.

Claims 24-26, 28-32, 103, 105-109, 111-113, 115, 116, 118-122, 124, 125, 136-150 and 152-160 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor, at the time the application was filed, had possession of the claimed invention. The Examiner's stated rationale for this rejection is substantially identical to the rationale for the rejection of record in the last substantive Office Action. (Office Action dated May 17, 2001 at paragraph 5.)

Applicant maintains that the subject matter of Claims 24-26, 28-32, 103, 105-109, 111-113, 116, 118-122, 124 and 125, and the subject matter of newly rejected Claims 136-150 and 152-160 is supported by adequate written description for the reasons stated in the Preliminary Amendment filed on November 19, 2001. The remarks addressing the prior rejection at pages 9-17 of the Preliminary Amendment filed on November 19, 2001, are incorporated herein by reference.

The Examiner deems the arguments presented in that Preliminary Amendment and the presented analysis in view of Example 14 of the Application of Guidelines to be unpersuasive. The Examiner believes that Example 14 is not germane to the claims under consideration because the rejected claims do not recite 95% identity. (Office Action dated April 7, 2003, at page 4.) Thus, Example 14 of the Application of Guidelines has been applied as a bright-line test to assess whether claims that recite percent amino acid sequence similarity are adequately supported by the specification.

Applying the Application of Guidelines in this way is legally improper because "[t]he inquiry into whether the description requirement is met is a question of fact that must be determined on a case-by-case basis." (MPEP § 2163(II)(A) at 2100-163, quoting In re Smith, 173 USPQ 679, 683 (CCPA 1972).) The Application of Guidelines are not a bright line test, but illustrate the analysis that should be applied, in view of the particular facts and circumstances of

each case, when determining whether the claimed invention is adequately described. Enzo Biochem Inc. v. Gen-Probe Inc., 63 USPQ2d 1609, 1613 (Fed. Cir. 2002).

Although the rejected claims do not recite "95% identity," they are similar to the claim in Example 14 of the Application of Guidelines because they define the primate or human MAdCAM by structural features (*e.g.*, at least about 55%, 75% or 90% amino acid sequence similarity to a recited amino acid sequence) and further define the primate or human MAdCAM or binding fragment thereof by function (*i.e.*, binds $\alpha 4\beta 7$ integrin). In addition, this application contains a more extensive written description of the claimed invention than the specification in Example 14 of the Application of Guidelines. For example, this application discloses three species of naturally occurring primate MAdCAM proteins by amino acid sequence (SEQ ID NO:2, 4 and 6) and nucleic acids encoding these proteins (SEQ ID NO:1, 3 and 5), methods suitable for assessing adhesion to $\alpha 4\beta 7$, and describes the broader class of naturally-occurring primate MAdCAM proteins by describing a combination of functional and structural features which are sufficient to distinguish the members of the genus from other materials. (See, *e.g.*, Specification at page 11, line 29 *et seq.*; and page 17, line 30 *et seq.*) Evidence that this description, and the claim language, is sufficient to distinguish the claimed nucleic acids from other materials, such as nucleic acids encoding murine MAdCAM, is provided in the specification.

> Nucleotide alignments revealed 81.9% sequence similarity between mouse and rat MAdCAM-1 cDNAs, 41.8% similarity between mouse and macaque cDNAs, 42.1% similarity between murine and human (Clone 4) MAdCAM-1 cDNAs, and 41.8% similarity between murine and human (Clone 20) MAdCAM-1 cDNAs. ...
>
> The amino acid sequence similarities were determined to be 78.5% between mouse and rat MAdCAM-1, 44.3% between mouse and macaque, and 39% between murine and MAdCAM-1 encoded by human Clone 4.

(Specification at page 57, line 32 through page 58, line 12.)

In view of these teachings, the subject matter of the rejected claims is described with a degree of particularity that is sufficient to distinguish it from other things.

In addition, the application contains a detailed disclosure of the structure of primate MAdCAM and relationships between structure and $\alpha 4\beta 7$ integrin binding function that is

sufficient to demonstrate that Applicant was in possession of the subject matter of the rejected claims at the time the application was filed. (Specification at page 17, line 30 through page 22, line 24.) In particular, the application contains a detailed description of the domain structure of murine, human and macaque MAdCAM proteins, and discloses that the amino-terminal immunoglobulin-like domains of the murine protein are involved in $\alpha 4\beta 7$ integrin binding, and that these domains of primate MAdCAM are likely to be involved in $\alpha 4\beta 7$ integrin binding. (Specification at page 18, line 22 through page 20, line 20.) Further, the application discloses the presence of a conserved "(G)LDTSL motif" in domain one of murine MAdCAM-1 and primate MAdCAM, that this motif is an integrin binding site, and that murine MAdCAM-1 requires this conserved motif for integrin binding. (Specification at page 19, line 19 through page 20, line 19.) The application further discloses that some or all of the sequences in the mucin domain of primate MAdCAM can be deleted without abrogating integrin binding. (Specification at page 21, lines 31 through page 22, line 9.)

This disclosure informs the person of ordinary skill in the art of the relationship between the structure of primate MAdCAM and $\alpha 4\beta 7$ integrin binding activity. In view of this disclosure, and the disclosure of the reduction to practice of three species of naturally occurring primate MAdCAM, the person of ordinary skill in the art would immediately be able to envision a large number of variants of primate MAdCAM that fall within the claims, and conclude that Applicant was in possession of the claimed subject matter.

The written description requirement is satisfied when the specification describes the claimed invention in sufficient detail so that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. Vas-Cath, Inc. v. Mahurkar, 19 USPQ2d 1111 (Fed. Cir. 1991). Applying the analysis illustrated in Example 14 of the Application of Guidelines to the particular facts and circumstances of this application compels a finding that the written description requirement for the subject matter of Claims 24 and 107 which recite "at least about 55% amino acid sequence similarity," Claims 103, 109, 113, 120 and 122 which recite "at least about 75% amino acid sequence similarity," Claims 105 and 115 which recite "at least about 75% nucleotide sequence similarity," Claims 136, 145, 149, 154 and 157-159 which recite "at least about 90% amino acid sequence similarity," Claims 106, 116, 144 and 150 which recite "at least about 90% nucleotide sequence similarity" and claims dependent from these claims is

satisfied, because one skilled in the art would reasonably conclude that Applicant had possession of the claimed invention at the time the application was filed.

Paragraph 6. Rejection of Claims 24-26, 28-32, 103, 105-109, 111-113, 115, 116, 118-122, 124, 125, 136-150 and 152-160 Under 35 U.S.C. § 112, First Paragraph.

Claims 24-26, 28-32, 103, 105-109, 111-113, 115, 116, 118-122, 124, 125, 136-150 and 152-160 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. The rejection is substantially the same as the rejection of Claims 107-113 and 121-135 at paragraph 6 of the Office Action dated May 17, 2001.

The Examiner states that the art recognizes that the effects of amino acid changes are not predictable. (Office Action at page 6.) The Examiner concludes that in view of this alleged unpredictability, it would require undue experimentation to practice the claimed invention based on the teachings of the specification. (Id.) Concerning the Briskin declaration, the Examiner states that the declaration discloses the results of studies performed using techniques that are not disclosed in the specification. (Id.) The Examiner interprets the Briskin declaration as demonstrating that the effect of amino acid substitutions on binding to $\alpha 4\beta 7$ integrin-binding could not be predicted. (Id.)

Applicant maintains that the claimed invention is enabled for the reasons stated in the Preliminary Amendment filed on November 19, 2001. "Enablement is not precluded by the necessity for some experimentation such as routine screening." In re Wands, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). "[A] considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." Id. Enablement does not require absolute predictability, but that the person of ordinary skill in the art be able to practice the invention without undue experimentation. Id. Factors to be considered in determining if an invention is enabled included (1) the nature of the claimed invention, (2) the breadth of the claims, (3) the relative skill in the art, (4) the state of the prior art, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary to make or use the invention, (7) the amount of direction or guidance presented in the application, and (8) the predictability or

unpredictability of the art. Id. No one factor is determinative. However, the enablement requirement is met if a preponderance of the evidence indicates that it is more likely than not that any person skilled in the art at the time the application was filed could have produced the claimed fusion proteins without undue experimentation.

The nature of the claimed invention and breadth of the claims.

The claims are drawn to fusion proteins or hybrid immunoglobulins. The claimed fusion proteins or hybrid immunoglobulins comprise a naturally occurring primate MAdCAM or an $\alpha4\beta7$ integrin-binding fragment thereof, a naturally occurring human MAdCAM or an $\alpha4\beta7$ integrin-binding fragment thereof, a primate MAdCAM moiety, or a primate MAdCAM or $\alpha4\beta7$ integrin-binding portion thereof. The claims recite that the naturally occurring primate or human MAdCAM, primate MAdCAM moiety or primate MAdCAM has a stated amount of amino acid sequence similarity (at least about 55%, 75% or 90%) to a recited amino acid sequence, or is encoded by a nucleic acid having a stated amount of nucleotide sequence similarity (at least about 75% or 90%) to a recited nucleotide sequence, and binds $\alpha4\beta7$ integrin.

The relative skill in the art and the state of the prior art.

The relative skill in the art of molecular biology at the time the application was filed was high. At that time, it was routine for the person skilled in the art to produce recombinant proteins and fusion proteins, and to assess binding function of proteins and fusion proteins (*e.g.*, immunoglobulin superfamily proteins such as MAdCAM) using conventional methods. A variety of suitable methods for producing and evaluating the binding activity of such proteins were well-known in the art at that time. (See, *e.g.*, Specification at page 15, line 22 through page 17, line 29 and references cited.)

Several immunoglobulin superfamily adhesion receptors are in the prior art, including VCAM-1, ICAM-1 and murine MAdCAM. The binding specificities of these immunoglobulin superfamily adhesion receptors was known at the time the application was filed. (See, *e.g.*, Specification at page 3, line 4 through page 5, line 4 and references cited.) The domain structures of these immunoglobulin superfamily adhesion receptors and sequence motifs required

for integrin-binding were also known in the art. (See, *e.g.*, Specification at page 19, line 11 through page 20, line 19, and references cited.)

The presence of working examples.

The specification discloses the nucleotide sequences of two nucleic acids encoding human MAdCAMs (SEQ ID NOS: 1 and 3), the nucleotide sequence of a nucleic acid encoding macaque MAdCAM (SEQ ID NO:5) and the amino acid sequences of the encoded proteins (SEQ ID NOS:2, 4 and 6). The specification also exemplifies adhesion assays using cells that express the MAdCAM proteins.

The specification discloses and exemplifies two fusion proteins that each comprise an $\alpha4\beta7$ binding fragment of human MAdCAM, and a method for identifying fusion proteins that bind $\alpha4\beta7$ integrin. (Specification at page 74, line 19 *et seq.*) One of the exemplified fusion proteins comprises the extracellular domain of human MAdCAM (SEQ ID NO:4) and the other comprises the two amino-terminal immunoglobulin-like domains of human MAdCAM (SEQ ID NO:4). The specification also discloses that these fusion proteins stained cells that express $\alpha4\beta7$ integrin. (Example 3, at page 73-76.)

The amount of direction or guidance presented in the application and the quantity of experimentation necessary to make or use the invention.

The person of ordinary skill in the art would be able to practice the claimed invention following the guidance of the specification and using no more than routine experimentation. Methods suitable for preparing variants of proteins that contain amino acid additions, deletions and/or substitutions were well known in the art at the time the application was filed. As discussed above, the specification includes working examples of two fusion proteins that each comprise an $\alpha4\beta7$ binding fragment of human MAdCAM, and a method for identifying fusion proteins that bind $\alpha4\beta7$ integrin. (Specification at page 74, line 19 *et seq.*)

The specification contains adequate guidance to enable a person skilled in the art to make the claimed fusion proteins. The specification includes a detailed discussion of MAdCAM structure at page 17, line 30 through page 22, line 24. This discussion points out regions and

particular amino acid motifs of MAdCAM that are important for α4β7 integrin binding. In particular, human and macaque MAdCAM are taught to have two amino-terminal immunoglobulin-like domains that are homologous to those of murine MAdCAM. (Specification at page 18, lines 21-26.) The specification teaches that domain 1 of murine MAdCAM and ICAM-1, ICAM-2 and ICAM-3, and domains 1 and 4 of VCAM-1 contain a short amino acid motif (G-(I/L)-(D/E)-(T/S)-(P/S)-L) that is located between β sheets c and d of the proteins (the C-D loop). (Specification at page 19, lines 19-29.) The specification further teaches that this GLDTSL motif is also found in the primate and human MAdCAMs disclosed in the application. Id.

The specification includes a discussion of published studies that demonstrated that mutations in the GLDTSL motif in ICAM-1 or VCAM-1 dramatically affected binding to LFA-1 or α4β7 integrin, respectively. (Id.) The specification further teaches that a mutation in the GLDTSL motif in murine MAdCAM abolished interaction with cells that expressed α4β7 integrin, and that the GLDTSL motif is required for binding of murine MAdCAM to α4β7 integrin. (Id. at page 20, lines 11-19.) The specification also teaches that each primate clone disclosed contains "a sequence of nine amino acids (which contains the "LDTSL" motif) in the predicted C-D loop of the Ig-like domain 1, and is implicated as a general integrin recognition site ...." (Id. at page 20, lines 31-34.)

Thus, the specification teaches the person of ordinary skill in the art that the C-D loop in immunoglobulin-like domain 1, and the GLDTSL motif or LDTSL motif in particular, are important for binding to α4β7 integrin and that amino acid additions, deletions and/or substitutions in the C-D loop could alter and possibly abrogate binding to α4β7 integrin. Accordingly, the specification provides ample guidance regarding the structure-function relationship of MAdCAM to enable any person skilled in the art to make the claimed fusion proteins without undue experimentation.

The predictability or unpredictability of the art.

The Examiner considers the art to be unpredictable. However, the patent statutes do not require absolute predictability, only that it would not require undue experimentation to make and use the claimed invention.

In view of the foregoing, the application satisfies the enablement requirement because any person skilled in the art at the time the application was filed could have made and used the claimed invention by following the teachings, guidance and examples of the application and his knowledge of the art without undue experimentation. At the time the application was filed, preparing and screening proteins, such as fusion proteins, to ascertain binding properties was routine in the art, and did not constitute undue experimentation. This type of routine screening is analogous to the screening of hybridomas to identify those hybridomas that produce a desired antibody which the Wands court determined was not undue experimentation. Wands, 8 USPQ2d at 1400, 1405 (holding that the claimed antibodies could be made without undue experimentation when antibodies produced by only 4 out of 143 hybridomas, or 2.8 percent, were proved to fall within the claims, and the antibodies proved to fall within the claims were isolated from only 2 out of 10 fusion experiments that were performed.) Moreover, objective evidence that it would not have required undue experimentation to make and use the claimed invention is provided by the Briskin Declaration.

Briskin Declaration

The Examiner states that the declaration discloses the results of studies performed using techniques that are not disclosed in the specification, and interprets the Briskin Declaration as demonstrating that it is unpredictable whether a primate MAdCAM that contains an amino acid replacement would bind $\alpha 4\beta 7$ integrin. However, the Briskin Declaration provides evidence that any person skilled in the art could have produced the claimed fusion proteins following the guidance provided in the specification and conventional techniques without undue experimentation.

The methods employed in the studies described in the Briskin Declaration were disclosed in the application or art-known at the time the application was filed. Methods that were art-

known need not be disclosed in a patent application. For example, the specification teaches and exemplifies methods for producing fusion proteins comprising α4β7 integrin-binding fragments of human MAdCAM and assessing α4β7 binding. (Example 3, at page 73-76.) In addition, suitable methods for introducing amino acid substitutions (*e.g.*, substituting a desired amino acid residue with alanine) were well-known and conventional in the art at the time the application was filed.

The Briskin Declaration describes a study in which a number of fusion proteins comprising portions of human MAdCAM that contained single amino acid substitutions were prepared and tested for binding to α4β7. The mutations were made in portions of human MAdCAM that correspond to regions of other immunoglobulin-like adhesion molecules that were known to be important for integrin binding, namely the CD loop, EF loop, C'E loop and FG loop. (Specification at page 19, line 19 through page 20, line 19; Declaration at page 4, lines 22-26.) Of the 31 fusion proteins generated, 14 displayed mean binding to α4β7 integrin at 80% to 100% of the control in an adhesion assay. (Declaration at Paragraph 5 (emphasis added.)) Thus, even though the study specifically introduced amino acid substitutions into regions of human MAdCAM that the specification teaches are important for binding to α4β7 integrin, about half of the fusion proteins produced retained at least 80% of the α4β7 binding activity. (Emphasis added.) Under these circumstances, like in Wands were the court held the claims to be enabled even though only 2.8 percent of antibodies tested were proved to fall within the claims, any experimentation required to practice the invention would not have been undue.

Reconsideration and withdrawal of the rejection is requested.

Paragraph 7. Priority Claim

The Examiner states that the claimed inventions are not disclosed in U.S. Patent Application No. 08/386,875. This application does not claim priority to U.S. Patent Application No. 08/386,875, and the Related Applications paragraph has been amended to delete reference to U.S. Patent Application No. 08/386,875.

Paragraph 9. Rejection of Claims 24-26, 28-31, 103, 105-109, 111, 113, 115, 116, 118, 120-122, 124, 136-142, 144-147, 149, 150, 152, 154, 155 and 157-160 Under 35 U.S.C. § 103(a).

Claims 24-26, 28-31, 103, 105-109, 111, 113, 115, 116, 118, 120-122, 124, 136-142, 144-147, 149, 150, 152, 154, 155 and 157-160 are rejected under 35 U.S.C. § 103(a) as being obvious over Butcher *et al.* (WO 94/13312, Reference AD of record) in view of Vonderheide *et al.* (U.S. Patent No. 5,599,676, Reference AB or record) and Erle *et al.* (*J. Immunol. 153*:517-528 (1994); Reference AX3 of record). The Examiner states that Butcher *et al.* teaches murine MAdCAM/Ig constant region fusion proteins, but does not teach primate or human MAdCAM fusion proteins. Erle *et al.* is said to teach that human MAdCAM binds α4β7 integrin and human cell lines expressing α4β7 and MAdCAM. Vonderheide *et al.* teach methods to isolate nucleic acids encoding molecules that bind α4β7. The Examiner concludes that it would have been obvious to make the claimed invention because Butcher *et al.* teach murine MAdCAM/Ig fusion proteins and Vonderheide *et al.* and Erle *et al.* provide the means to produce human or primate MAdCAM protein. The Examiner states that the person of ordinary skill in the art would have been motivated to modify the teachings of the references because Butcher *et al.* teach that MAdCAM fusion proteins that bind α4β7 could have been used for a variety of purposes.

Vonderheide *et al.* discloses and claims a general method for isolating a cDNA that encodes an α4 integrin receptor. However, there is no mention of human MAdCAM or disclosure of any α4 integrin receptors in Vonderheide *et al.*

Erle *et al.* does not teach that human MAdCAM binds to α4β7. Erle *et al.* expressly teaches that the human homologue of MAdCAM-1 had not been identified, and consequently transfected cells that expressed murine MAdCAM-1 were used in their experiments. (Erle *et al.* at page 525, left column.)

The cited references do not create a prima facie case.

The claimed invention is not obvious over the cited references, because none of the references either individually or in combination suggests the claimed fusion proteins. A finding that the claimed invention is obvious under 35 U.S.C. § 103 requires that (1) "the prior art would

have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process;" and (2) that "the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success." In re Vaeck, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991). Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in Applicant's disclosure. Id. When novel compounds are claimed using structural terms, a *prima facie* case of obviousness requires that the prior art suggest the claimed compounds themselves to the person of ordinary skill in the art. In re Deuel, 34 USPQ2d 1210, 1214 (Fed. Cir. 1995). A particular result is not made obvious by a general incentive or the existence of techniques suitable to achieve the result. Id., at 1216.

The disclosure of Butcher *et al.* does not suggest the claimed fusion proteins to the person of skill in the art or provide a reasonable expectation of success, because murine MAdCAM and primate or human MAdCAM have a very low degree of sequence similarity, and cDNAs encoding these proteins do not cross hybridize. Butcher *et al.* establishes that murine MAdCAM, nucleic acids encoding murine MAdCAM and general methods for isolating and cloning nucleic acids encoding adhesion molecules were known to exist at the time the invention was made. However, primate or human MAdCAM and murine MAdCAM have a very low degree of sequence similarity. In fact, cDNAs encoding murine MAdCAM and primate MAdCAM have such a low degree of sequence similarity that initial attempts to isolate a cDNA encoding primate MAdCAM by low stringency cross-hybridization with a nucleic acid encoding murine MAdCAM -1 were unsuccessful. Evidence is provided by Shyjan A.M. *et al., J. Immunol. 156*:2851-2857 (1996) (Reference AX4 of record), a later article coauthored by Applicant. Shyjan *et al.* teach that "[i]nitial attempts to clone the human homologue to murine MAdCAM -1 by low stringency cross-hybridization suggested that nucleotide conservation between murine MAdCAM -1 and higher species was poor." (Shyjan *et al.*, at page 2853, left column.)

Further evidence that primate MAdCAMs are structurally distinct from murine MAdCAM is provided in the specification where it is disclosed that mouse MAdCAM and rat MAdCAM have 78.5% amino acid sequence similarity, but that the amino acid sequences of mouse MAdCAM and macaque MAdCAM (SEQ ID NO:6) are only 44.3% similar, and that the amino acid sequences of murine MAdCAM and human MAdCAM-1 encoded by human clone 4

(SEQ ID NO:2) are only 39% similar. (Specification, at page 49, lines 18-21.) Similarly, the specification discloses that cDNAs encoding mouse MAdCAM and rat MAdCAM have 81.9% nucleotide sequence similarity, but that the degree of nucleotide similarity between cDNAs encoding mouse MAdCAM and macaque MAdCAM (SEQ ID NO:5) is only 41.8%, mouse MAdCAM and human MAdCAM clone 4 (SEQ ID NO1) is only 42.1%, and mouse MAdCAM and human MAdCAM clone 20 (SEQ ID NO:3) is only 41.8%. (Specification, at page 49, lines 9-14.)

The secondary references, Vonderheide *et al.* and Erle *et al.*, do not remedy the defect in the teachings of Butcher *et al.* As pointed out above, Vonderheide *et al.* discloses and claims a general method for isolating a cDNA that encodes an α4 integrin receptor. There is no mention of primate or human MAdCAM or disclosure of the amino acid sequence (or nucleotide sequence encoding) of any α4 integrin receptors in Vonderheide *et al.* In addition, Erle *et al.* does not teach that human MAdCAM binds to α4β7. Erle *et al.* expressly teach that the human homologue of MAdCAM-1 had not been identified, and consequently they used transfected cells that expressed murine MAdCAM-1 in their experiments. (Erle *et al.*, at page 525, left column.) Therefore, at best, Vonderheide *et al.* discloses a method suitable for isolating a cDNA that encodes an α4 integrin receptor, and Erle *et al.* demonstrates that primate or human MAdCAM was not known.

The cited references teach the amino acid sequence of murine MAdCAM, a sequence that has only limited sequence similarity to primate or human MAdCAM (Butcher *et al.*), a belief that human or primate MAdCAM is likely to exist and bind α4β7 integrin (Erle *et al.*), and the existence of a possible method for cloning receptors for α4 integrins (Vonderheide *et al.*). These teachings do not establish a *prima facie* case of obviousness against the claimed fusion proteins, because the amino acid sequence disclosed by Butcher *et al.* is so dissimilar from the amino acid sequence of primate or human MAdCAM that it cannot be deemed to reasonably suggest the claimed fusion proteins. Moreover, the cited references are devoid of any nucleotide sequence data, any amino acid sequence data or any other teachings that would have reasonably suggested the particular claimed fusion proteins to the person of ordinary skill in the art. The combined teachings of the references do not create a *prima facie* case, because they do not suggest the

claimed fusion proteins.

The cited references might, at best, demonstrate the existence of a general incentive and techniques that might be suitable to arrive at the claimed invention. However, a general incentive and existence of suitable technology is not sufficient to establish a *prima facie* case of obviousness. Deuel, 34 USPQ2d at 216. A prior art teaching that would reasonably suggest the particular claimed nucleic acids to the person of ordinary skill in the art and provide a reasonable expectation of success is required. But the cited references do not meet this standard and merely demonstrate that primate or human MAdCAM was not known at the time the application was filed, and disclose a method that might have been used to obtain a nucleic acid encoding primate or human MAdCAM if they existed. Thus, the cited combination of references creates nothing more than a hope or, at best, a research plan that might have led the person of ordinary skill in the art to isolate the claimed nucleic acids. According to Deuel, such a hope or research plan does not reasonably suggest the claimed fusion proteins themselves, particularly when, as here, primate and human MAdCAM have very limited sequence similarity to prior art murine MAdCAM. Id.

The rejection is inconsistent with mandatory legal authority.

The rejection is inconsistent with Deuel and Ex parte Goldgaber, 41 USPQ2d 1172 (Bd. Pat. App. & Inter. 1995), because the disclosure in the cited references does not establish a *prima facie* case and would not have led inevitably to the claimed fusion proteins. Deuel unambiguously articulates a fundamental rule of law for analyzing obviousness under 35 U.S.C. § 103: the existence of technology that is suitable for producing a novel composition does not on its own render that novel composition obvious. Id. at 1216. Therefore, Deuel controls the analysis in this application, even though the ultimate question of obviousness under § 103 is determined on the particular facts of this case. Goldgaber and Deuel agree on this point.

> We are mindful of the holding in Bell, and the recently issued opinion In re Deuel, ... reaffirming the principle that a general method of isolating cDNA or DNA molecules is essentially irrelevant to the question of whether the specific molecules themselves would have been obvious, in the absence of other prior art that suggests the claimed DNAs.

Goldgaber, 41 USPQ2d 1172, 1176 (Bd. Pat. App. & Inter. 1995).

In Deuel, the application at issue disclosed the purification and characterization of "heparin-binding growth factor" (HBGF) from bovine uterine tissue, and disclosed the amino acid sequence of the first 25 N-terminal amino acids of HBGF. Deuel, 34 USPQ2d at 1212. The application also disclosed the nucleotide sequence of a bovine and a human cDNA encoding HBGF. Id.

Claims drawn to nucleic acids encoding human heparin-binding growth factor were rejected by the Examiner under 35 U.S.C. § 103 as being obvious over a reference that disclosed the first 19 amino-terminal amino acids of a "heparin-binding brain mitogen" ("Bohlen") and a reference that described a method for isolating DNAs or cDNAs by screening a DNA or cDNA library with a gene probe ("Maniatis"). Id. at 1212-1214. The 19 amino acid sequence disclosed by Bohlen matched the first 19 amino acids of the N-terminal amino acid sequence disclosed in Deuel's application. Id. at 1213. The court reversed the rejection stating:

> Because Deuel claims new chemical entities in structural terms, a *prima facie* case of unpatentability requires that the teachings of the prior art suggest *the claimed compounds* to a person of ordinary skill in the art.

Id. at 1214. The court further stated:

> A general incentive does not make obvious a particular result, nor does the existence of techniques by which those efforts can be carried out. Thus, Maniatis's teachings, even in combination with Bohlen, fail to suggest the claimed invention.

Id. at 1216.

In Goldgaber, the Board distinguished Deuel and held that claims drawn to a nucleic acid which hybridizes to message for beta-amyloid polypeptide of Alzheimer's disease and which hybridizes with an oligonucleotide probe having a nucleotide sequence disclosed in Figure 1 of the application, were rejected as obvious over Glenner *et al.* (U.S. Patent No. 4,666,829; "Glenner") and Huynh *et al.* ("Huynh"). Goldgaber, 41 USPQ2d at 1173. The Board, clearly mindful of Federal Circuit precedent, correctly set a high standard for distinguishing Bell and Deuel that focuses on the specific teachings of the cited references and the results that those teachings would inevitably produce. Id., at 1174-1177.

In Goldgaber, the primary reference, Glenner, disclosed the amino acid sequence of Alzheimer's Amyloid Polypeptide (AAP), the sequences of two sets of oligonucleotide probes suitable for isolating a gene that encodes AAP, methods for performing hybridization reactions, and use of the oligonucleotides in diagnostic assays. Id. at 1173. The oligonucleotide probes were said to be targeted to areas of low degeneracy in the AAP sequence, and designed to have the highest degree of specificity for the cDNA encoding AAP that could be attained under the circumstances. (Glenner, at column 9, lines 30-62.) Huynh disclosed methods for constructing and screening cDNA libraries. Id. Figure 1 of Goldgaber's application included an illustration of the nucleotide sequence encoding beta-amyloid polypeptide and the amino acid sequence of the beta-amyloid polypeptide. Id. The amino acid sequence of the beta-amyloid polypeptide illustrated in Figure 1 of Goldgaber's application is the same as the amino acid sequence of AAP disclosed in Glenner. Id. (See also, Glenner, at column 6.)

The Board found that Glenner disclosed "clearly and unequivocally that it *is* possible to ascertain the base sequence of the gene coding for AAP, ... [and] the meaning [sic] for accomplishing that result, *i.e.*, two sets of fully degenerate probes." Id. at 1176. The Board also found that Glenner put the person of skill in the art in possession of the probes which it characterized as being the key to success. Id., at 1174. The Board found that combined teachings of Glenner and Huynh "would have led inevitably to a clone of DNA meeting the limitations recited in claim 4," and stated that "Glenner puts the key in the lock of the door of success." Id., at 1175 (emphasis added).

The Board also found factual distinctions between the teachings of Glenner and Huynh and the teachings of the references in Bell and Deuel.

> Conspicuous by its absence from Rinderknecht or Bohlen [the primary references in Bell and Deuel, respectively] is any teaching relating to DNA, cDNA or the gene coding for the polypeptide of interest. Not only is the "primary" reference Glenner more comprehensive than the primary references in *Bell* or *Deuel*, but the "secondary" reference Huynh is also stronger than the secondary references in those cases.

Id., at 1176.

The Board affirmed the rejection under 35 U.S.C. § 103 and distinguished Deuel

stating:

> The facts before us, however, present a different issue [than was presented in Deuel] and a more compelling case of obviousness because Glenner discloses more than the amino acid sequence of AAP. Glenner constructs a "bridge" of information leading from the polypeptide AAP via the oligonucleotides corresponding to its amino acid sequence to the gene coding for AAP.

Id. at 1177 (emphasis added).

> Glenner puts a person having ordinary skill in possession of two sets of fully degenerate probes, and Huynh discloses specific information pertaining to the construction and screening of a suitable cDNA library. The information in the Glenner patent, when combined with the Huynh reference, provide a reasonable expectation of success which is all that is required for obviousness under 35 USC 103.

Id. (emphasis added). Thus, the Board distinguished Deuel based upon the disclosure of oligonucleotide probes in Glenner, which provided a "bridge" of information that would have "led inevitably" to the claimed nucleic acid, and articulated a high standard for distinguishing Bell and Deuel that focuses on the specific teachings of the cited references, and the results that those teachings would inevitably have produced. Id., at 1174, 1177.

Like in Deuel, this application claims new chemical entities (*i.e.*, proteins) in structural terms, and Butcher *et al.*, Vonderheide *et al.* and Erle *et al.* are devoid of any teachings relating to the particular claimed proteins or nucleic acids encoding them. Deuel makes clear that incentive does not make obvious a particular result, nor does the existence of techniques by which those efforts can be carried out. Deuel, 34 USPQ2d at 1216.

The facts of this application militate against a finding of obviousness more strongly than the facts in Deuel. In Deuel, the cited prior art disclosed a 19 amino acid sequence that matched the first 19 amino acids of the N-terminal amino acid sequence disclosed in Deuel's application. Id., at 1213. But the prior art in this case contains no amino acid sequence data, no nucleotide sequence data, and no other teaching that relates to the particularly claimed nucleic acids. The absence of amino acid sequence or nucleotide sequence data from the prior art is evidence of nonobviousness, because it places the person of skill in the art further away from the claimed

nucleic acids than he was in Deuel, with nothing to point him toward the particular claimed nucleic acids.

This application is unlike Goldgaber, because it does not present facts that can be distinguished from Deuel. Critical to the Board's decision in Goldgaber was the disclosure in Glenner of the nucleotide sequences of two sets of oligonucleotide probes targeted to areas of low degeneracy in the AAP, methods for performing hybridization reactions, and use of the oligonucleotides in diagnostic assays. Goldgaber, 41 USPQ2d at 1177. The Board viewed these teachings as forming a "bridge" of information that "led inevitably" to the claimed nucleic acid. Id. at 1174, 1177. There is no such bridge in this case.

Vonderheide *et al.* does not provide the "bridge" because it lacks the specificity required to provide a reasonable expectation that the disclosed and claimed method, combined with the teachings of Butcher *et al.* and Erle *et al.*, would have "led inevitably" to the claimed fusion proteins that comprise primate or human MAdCAM (or $\alpha4\beta7$ integrin-binding portions thereof). The method of Vonderheide *et al.* is a general method which is taught to be suitable for isolating a cDNA that encodes any receptor that binds $\alpha4$ integrins, which include but are not limited to $\alpha4\beta1$, $\alpha4\beta7$ and $\alpha4$ itself, under the conditions recited in the claims. (Vonderheide *et al.* at column 4, lines 27-32.) These general teachings are very different from the disclosure in Glenner of specific oligonucleotide probes targeted to areas of low degeneracy and designed to have the highest degree of specificity for the cDNA encoding AAP that could be attained under the circumstances. (Glenner at column 9, lines 30-62.)

The rejection is inconsistent with Deuel and Goldgaber and should be withdrawn, because the cited prior art in this case contains no amino acid sequence data, no nucleotide sequence data, and no other teaching that relate to primate or human MAdCAM or the claimed fusion proteins. Thus, the person of ordinary skill in the art is further away from the claimed invention than he was in Deuel, with nothing to point him toward the claimed proteins. Furthermore, unlike in Goldgaber, the teachings of the cited references do not have a degree of specificity that would have "led inevitably" to the claimed fusion proteins.

Reconsideration and withdrawal of the rejection are requested.

Paragraph 10. Rejection of Claims 32, 112, 119, 125, 143, 148, 153 and 156 Under 35 U.S.C. § 103(a).

Claims 32, 112, 119, 125, 143, 148, 153 and 156 are rejected under 35 U.S.C. § 103(a) as being obvious over Butcher *et al.* (WO 94/13312, Reference AP of record) in view of Vonderheide *et al.* (U.S. Patent No. 5,599,676, Reference AB of record) and Erle *et al.* (*J. Immunol. 153*:517-528 (1994); Reference AX3 of record), and further in view of Capon *et al.*

The Examiner did not provide additional information to further identify the Capon *et al.* reference, but it appears that he intended to cite Capon *et al.*, U.S. Patent No. 5,565,335 (Reference AF of record) which was cited in the Office Action dated August 26, 1999. The Examiner is requested to confirm this, or to clarify the rejection in the next Office Communication.

Butcher *et al.*, Vonderheide *et al.* and Erle *et al.* are cited for the teachings discussed in the rejection at Paragraph 9. Capon *et al.* is said to teach Ig fusion protein homodimers.

The claims are not obvious for the reasons discussed with respect to the rejection at Paragraph 9. Capon *et al.* adds nothing to the rejection because Capon *et al.* contains no teachings that relate to primate or human MAdCAM or to the claimed fusion proteins.

Reconsideration and withdrawal of the rejection are requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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